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Review

Exercise, Inflammation and Aging

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ABSTRACT: Aging results in chronic low grade inflammation that is associated with increased risk for disease, poor physical functioning and mortality. Strategies that reduce age-related inflammation may improve the quality of life in older adults. Regular exercise is recommended for older people for a variety of reasons including increasing muscle mass and reducing risk for chronic diseases of the heart and metabolic systems. Only recently has exercise been examined in the context of inflammation. This review will highlight key randomized clinical trial evidence regarding the influence of exercise training on inflammatory biomarkers in the elderly. Potential mechanisms will be presented that might explain why exercise may exert an anti-inflammatory effect.

Key words: Aging; Exercise, Inflammation; Adipose; Elderly

Inflammaging: the role of inflammation in age-related disease.

Aging is associated with increased inflammation

Chronic low-grade systemic inflammation is a common manifestation of aging. Two to four-fold elevations in circulating levels of pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α, and acute phase proteins such as C-reactive protein (CRP) and serum amyloid A (SAA), are typical in the elderly when compared to the young, even in the absence of chronic disease[1]. There are several potential mechanisms responsible for age-associated inflammation that have been examined. Moreover, strategies aimed at dampening inflammation in elderly subjects, including pharmacological therapies and lifestyle factors, have often produced equivocal results. The primary purpose of this review is to examine the literature regarding the effects of exercise on inflammation in the elderly, and describe potential mechanisms for these effects.

Causes of inflammation with aging

Many mechanisms likely contribute to age-related inflammation. As with all other physiological systems, there are significant declines in immune function with aging that promote inflammation, but the chronic low grade inflammatory state in the elderly also is clearly a consequence of age-related chronic diseases[2]. A few of the major contributors will be briefly discussed below, recognizing that many of the factors that promote age-related inflammation are inter-related.

As people age, the prevalence of conditions associated with inflammation increase, such as obesity, physical inactivity[3], cardiovascular disease (CVD)[4], diabetes[5], chronic kidney disease[6], osteoarthritis[7], and Alzheimer's disease[8], making it difficult to decipher if these conditions are a cause or consequence of the excessive inflammation in the elderly. While several studies have shown that inflammatory biomarkers are increased in the elderly individuals in the absence of overt disease[9-11], others have failed to show any evidence of increases in inflammatory biomarkers in the healthy elderly[12, 13]. As suggested by Ferruci et al[14], this discrepancy may be due to differences in the actual health status of the subjects in

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these studies. In partial support of this, Ferruci showed that the presence of CVD risk factors and morbidity were shown to account for some, but not all, of the variation in inflammatory biomarkers in a cross-section of nearly 1,300 men and women aged 20 - 102 years in the general population. Taken together, these data highlight the complex interaction between aging, inflammation, and chronic disease.

Increases in oxidative stress with aging may also contribute to the development of chronic inflammation and disease. It is well established that aging is associated with increases in tissue and circulating levels of reactive oxygen species (ROS), as well as declines in antioxidant capacity[15]. There are a variety of potential mechanisms linking oxidative stress to inflammation, though substantial evidence is emerging that ROS activation of toll-like receptors on a variety of immune cells play an important role in activating the inflammatory cascade[16]. As a result, pharmacological therapies and lifestyle modifications designed to prevent oxidative stress could potentially have a significant impact on age-related inflammation.

While transient inflammation is necessary for recovery from injury and infection, it has been hypothesized that the excessive inflammation in aging may also be caused by an exaggerated acute-phase response that may be a cause or consequence of a delayed recovery from an insult that promotes inflammation. For example, both endotoxin administration and pneumococcal infection in elderly subjects result in exaggerated initial increases in inflammatory biomarkers such as CRP, TNF-α, and soluble TNF receptor-1 (TNFR-1). However, there is also a prolonged maintenance of the acute phase response and fever [17, 18], due in part to impaired clearance of these immune mediators. This suggests that at least under certain conditions the elderly are capable of mounting an adequate immune response, but are unable to completely terminate the response in a normal timeframe. This failure to completely resolve an immune response may contribute to the chronic state of low-grade inflammation associated with aging. Furthermore, chronic, low grade inflammation also may serve to prime the body to mount an exaggerated response to future insults that would normally be dampened if the immune system were not previously activated. Thus, a vicious cycle exists in which the incomplete resolution of previous immune responses in aging is responsible for promoting exaggerated future immune responses.

Strategies to reduce inflammation in the elderly

Due to the strong correlation between inflammation and the development and progression of many age-related chronic diseases, a variety of strategies have been utilized to minimize inflammation associated with aging. Pharmacological interventions may provide one alternative and it has been suggested that medications like fibrates, statins, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and non-steroidal anti-inflammatory drugs (NSAIDS) may have a clinical role in reducing inflammation, even though they may not be currently indicated to do so. (reviewed in [19]). However, the plethora of side effects common with these drugs, e.g., gastrointestinal distress and cardiovascular complications [20], as well as the additional financial burden associated with their use, have limited the utility of these treatments. Therefore, lifestyle interventions such as exercise training and dietary modifications may provide a low cost and long-term alternative to limit inflammation and slow declines in the elderly. Many dietary factors have been reported to confer anti-inflammatory benefits, and have been reviewed extensively elsewhere [21-26]. In short, reductions in caloric intake resulting in weight loss may provide one mechanism to dampen age-related inflammation [21]. Other research has focused on modifying nutritional components to reduce inflammation, such as micronutrients [22], macronutrients [23, 24], plant stanols and sterols [25], and a variety of prebiotics and other dietary components [26]. The remainder of this review will focus on the role that increasing physical activity and exercise training may play in attenuating age-related inflammation.

There is evidence that exercise can both cause and attenuate inflammation. Acute, unaccustomed exercise can cause muscle and connective tissue damage, especially if done at high intensities and for prolonged durations. This typically manifests as delayed onset muscle soreness which is preceded by microstructural skeletal muscle damage (e.g. streaming z disks), inflammatory cell infiltration and elevation of muscle-specific creatine kinase isoforms [27]. In some cases, inflammatory cytokines can be detected in peripheral blood of people after high intensity, unaccustomed exercise, especially if lengthening contractions are performed [28]. This damaging response is attenuated if exercise is done repeatedly as the tissue adapts to the new overload stress. Indeed, blocking the inflammatory response using broad spectrum anti-inflammatory drugs can reduce muscle adaptation and, ultimately, increases in muscle performance induced by the exercise [29]. On the other hand, many, but not all, studies have demonstrated that regularly performed cardiovascular exercise training may reduce markers of systemic inflammation [30, 31]. It is this literature that will be the focus of this review because of the strong association between elevated systemic inflammatory markers and

Table 1. Selected studies demonstrating the association between increased physical activity or physical fitness and inflammatory biomarkers in the elderly.

Reference	N	Age	Activity or Fitness Measure	Inflammatory Markers
Taaffe et al., 2000	880	74.3±2.7	Time in moderate or strenuous activity (hr/yr)	↓CRP, ↓IL-6
Geffken et al., 2001	5888	65 or older	Leisure time activity in previous two weeks (kcal/wk)	↓CRP
Wannamethee et al., 2002	3810	60-79	Physical Activity Index	↓CRP
Reuben et al., 2003	870	74.3	Modified Yale Physical Activity Survey (kcal/min)	↓CRP, ↓IL-6
Colbert et al., 2004	2964	70-79	Time and duration spent activity over previous year (kcal/kg/wk)	↓CRP, ↓IL-6, ↓TNFα
Albert et al., 2004	2833	>56	Number of times engaged in physical activity (times/wk)	↓ CRP
Elosua et al., 2005	1004	65 or older	Time spent in light and moderate activity	↓CRP, ↓IL-6, ↔IL-10, ↔IL1β, ↓IL1ra, ↓IL-18 **Men**↔sIL-6R, ↓TNFα **Women**↓sIL-6R, ↔TNFα
Rahimi et al., 2005	209	63±10	Peak MET level (METs)	↓CRP
Yu et al., 2009	3289	50-70	International Physical Activity Questionnaire (MET-hr/wk)	↓CRP, ↑adiponectin,↔ TNFαRII, ↔IL-6,
Valentine et al., 2009	132	70±5.4	VO_2 Peak (ml/kg/min)	↓ CRP men; ↔CRP women

↓=significant reduction; ↑=significant increase; ↔=no change; CRP=C-reactive protein; IL=interleukin; TNFα=tumor necrosis factor alpha; kcal=kilocalorie, MET=metabolic equivalent; wk=week; ml=milliliter, kg=kilogram.

chronic diseases of the aged [32]. Evidence regarding non-pharmaceutical means to reduce chronic inflammation would be important due to the potentially harmful side effects of medications.

Regular Exercise as a Means of Reducing Age-related Inflammation

Observational Studies

At least nine large cohort studies have been conducted in older individuals (average age of >60 years) that assessed the relationship between self reported physical activity levels and systemic markers of inflammation [32-40]. While there are a few exceptions [38, 41], the data consistently demonstrates an inverse, dose-response relationship between physical activity and inflammatory biomarkers, even at relatively modest activity levels (Table 1). Several factors clearly influenced the relationship between activity levels and inflammatory biomarkers in these studies, including gender, body composition, medication and supplement use, and the specific biomarkers assessed. Despite this, the relatively consistent findings from these diverse reports suggest a robust association between physical activity and markers of inflammation. Highlights and trends from these studies are described below.

Two of the larger cohort studies to examine the relationship between physical activity levels and inflammatory markers were the Cardiovascular Health (CH) Study [34] and the British Regional Heart (BRH) Study[35]. Combined, these studies collected self-reported physical activity data and measured CRP levels as well as other inflammatory and hemostatic variables in over 10,000 individuals, all greater than 60 years of age. In both studies, CRP levels were inversely related to physical activity levels, even after adjusting for multiple risk factors. Furthermore, it appears that the amount of exercise needed to lower CRP levels was relatively modest in these studies. For example, in the CH study, CRP levels were significantly lower in the 2nd lowest physical activity quartile in which total energy expenditure was estimated to be just 368 – 1050 kcal/week.

There appear to be disparate results from studies that measured other inflammatory markers, such as IL-6 and/or TNF-α. For example, in the MacArthur Study of Successful Aging, a large (N =880) cohort study of healthy elderly individuals (age 70 – 79 years), Taaffe et al [33] reported that both IL-6 and CRP were reduced as time spent doing moderate and strenuous physical activity increased. By contrast, in a cohort of 3300 older Chinese (average age = 60 years), Yu et al [40] found that higher levels of physical activity were related to lower levels of CRP, but not IL-6 or TNF-α. Similarily, in the Health Aging and Body Composition (ABC) study, Colbert et al [37] found an inverse relationship between activity levels and several inflammatory biomarkers, including CRP, IL-6 and TNF-α, although the correlation with TNF-α was no longer significant after adjusting for adiposity. Interestingly, anti-oxidant supplementation in this study was associated with lower inflammatory markers regardless of physical activity levels. Finally, in the InCHIANTI study [39], elderly individuals engaging in moderate-high amounts of physical activity, defined as at least 5 hours of moderate intensity (>4 METS) exercise/week, had lower levels of CRP and IL-6 compared to sedentary people. Moreover, even light activity (2-4 hours of walking-type activity/week) was associated with lower CRP in men, and IL-6 in women. Lastly, in a cohort of 870 elderly (aged 70 – 79), Reuben et al[36] showed that total recreational physical activity was inversely associated with both CRP and IL-6 levels. As with some of the previous studies mentioned, time spent in lighter activities like house and yard/work were also inversely related to CRP, though not IL-6, levels. This data suggests that CRP may be more responsive to physical activity levels than either IL-6 or TNF-α, though the data in this regard are not entirely consistent.

The association between physical activity levels and inflammation also has been influenced by gender and/or body composition in several studies. For example, in the Pravastatin Inflammation/CRP Evaluation (PRINCE) study, Albert et al[38] found no relationship between CRP and physical activity levels in elderly women. However, there was an inverse dose-response relation between CRP and physical activity levels in men, even after adjusting for BMI and other risk CVD risk factors. Interestingly, the reduction in CRP levels after 6 months of statin treatment were similar across physical activity groups. By contrast, Valentine et al [41] investigated the relationship between gender, body composition (measured by DXA), plasma CRP, and physical activity levels in healthy, community dwelling older adults. In both genders, CRP levels were positively correlated to measures of adiposity, after controlling for aerobic fitness and physical activity levels, but were not related to physical activity levels itself.

Only a few observational studies have examined the relationship between *exercise performance* or *aerobic fitness* and inflammatory biomarkers in those > 60 years of age [33, 41, 42], and the data from these studies are somewhat equivocal. Rahimi et al [42] found an inverse relationship between CRP levels and aerobic fitness in patients with angiographically documented coronary artery disease, including after adjustment for gender, BMI, and other CVD risk factors. In addition, Taaffe et al [33] found an inverse relationship between walking speed and IL-6 and CRP levels. However, Valentine et al [41] did not find any relationship between aerobic fitness and CRP levels in elderly men or women after adjusting for adiposity measures. The dearth of data comparing inflammatory biomarkers across fitness levels in elderly patients makes it difficult to draw definitive conclusions, and suggests that further research in this area may be warranted.

Though it is not possible to make conclusions about cause and effect from these observational studies, the preponderance of evidence from multiple large cohort studies strongly suggests a fairly robust inverse relationship between physical activity levels and biomarkers of inflammation. Of course, the data from many of these observational studies should be interpreted with caution based on the fact that most of the physical activity data was self-reported. However, while differences in subject characteristics make it difficult to compare the results from these studies, it appears that lower levels of CRP, and perhaps other markers, are commonly found in individuals engaging in very modest levels of activity.

Randomized controlled exercise trials and inflammation in the aged

Definitive evidence regarding the role of exercise on inflammation in the aged can only be ascertained from randomized clinical trials. Unfortunately, there have been very few such trials, especially in the aged, and the available data reflect less robust findings when compared to the cross-sectional studies mentioned above. While there have been several excellent review articles on the topic [43, 44], we will limit our discussion here to those studies which included only people over 60 years in age (Table 2).

Several studies from Nicklas's lab have examined the effects of exercise on blood markers of chronic inflammation. In a 2 x 2 randomized design, Nicklas et al (2004) examined the effects of 18 months of diet-induced weight loss and/or combined resistance training and walking 3 times/week on serum CRP, IL-6 and soluble TNF receptor 1 (sTNFr1) in 316 community-

Table 2. Selected RCCT's showing the effect of exercise training on inflammatory biomarkers in the elderly

Reference	N [+]	Age	Duration	Exercise Intervention	Inflammatory Marker
Kapasi et al., 2003	94 96	87±8 88±7	32 wk	Intermittent sessions of aerobic exercise, one episode of arm resistance training daily, 5x/wk	sTNFRII↔
Nicklas et al., 2004	67 70	69±6 69±6	18 mo	1 hour, walking 50-75% HRR and lower body resistance training with weighted cuff, 3x/wk	↔CRP, ↔IL-6, ↔IL-6sR, ↔TNFα, ↔sTNFRI & II
Hammett et al., 2004	30 31	66±4 67±5	6 mo	45 min, aerobic training estimated 80% of VO_2 Max, 4x/wk (3x supervised, 1x unsupervised)	↔CRP
Kohut et al., 2006	48 49	69.8±5.5 70.3±4.6	10 mo	45 min, aerobic exercise class at up to 65-80% VO_2 peak, 3x/wk	↓CRP, ↓IL-6, ↓IL-18*
Nicklas et al., 2008	183 186	76.4±4.1 77.0±4.4	12 mo	150 min/wk, walking at RPE 12-13, resistance training RPE 15-16	↔CRP, ↓IL-6
Vieira et al., 2009	66 61	70±0.8 70±0.6	10 mo	45-60 min, 60-70% VO_2 Max, 3x/wk	↓CRP
Campbell et al., 2009	53 62	60.5±7.0 60.9±6.8	12 mo	45 min, 60-75% HR max, 5x/wk (3x supervised, 2x unsupervised)	↓CRP, ↔IL-6
Beavers et al., 2010	182 186	76.4±4.1 77.0±4.4	12 mo	150 min/ wk walking goal at RPE 12-13, resistance training at RPE 15-16	↓IL-8, ↔TNFα,↔sTNFr I & II, ↔IL-6sR, ↔IL-1sRII, ↔IL-15, ↔adiponectin, ↔IL-1ra, ↔IL-2sRα

[+] top number experimental, bottom number control group; *TNFα was reduced in both groups
↓=significant reduction; ↑=significant increase; ↔=no change; CRP=C-reactive protein; IL=interleukin; TNFα=tumor necrosis factor alpha; kcal=kilocalorie, MET=metabolic equivalent; wk=week; ml=milliliter, kg=kilogram

dwelling overweight, older adults with radiographic evidence of knee osteoarthritis [45]. The subjects exhibited baseline elevations in CRP (~6-7 mg/L) indicative of chronic inflammation. They found that diet-induced weight loss, but not exercise, reduced CRP, IL-6 and sTNFr1. There was no interaction indicating that the lower levels of inflammatory proteins were due to diet treatment and not exercise in the combination group. There were no effects of treatment on soluble IL-6 receptor, TNF-α or soluble TNFr2. The decrease in CRP was greater in men than women. It is interesting to note that the diet groups lost significantly more body weight than the exercise only group. Indeed, they found that change in BMI was related to change in CRP and sTNFr1, but not IL-6. Therefore, data from this study support the idea that weight loss is needed to see significant reductions in chronic inflammation. While there were no exercise-training induced changes, it should be pointed out that the exercise group did have lower levels of CRP at 18 months post (-0.02 vs +0.96 µg/mL in control group). It could be that either a longer period of training or more intense training, perhaps resulting in greater weight (e.g. fat loss), is needed before the inflammatory lowering effects of exercise can be seen. It is important to point out that these subjects had knee osteoarthritis which could have limited their exercise adherence or intensity. Indeed, adherence to the exercise treatment was 60%, the lowest of any of the treatment groups (38). Lastly, it was unclear whether the treatment groups were equivalent in terms of anti-inflammatory medication usage.

In a parallel randomized group design, Nicklas et al (2008) examined the effects of 12 months of moderate walking training versus a health education attention control on plasma CRP and IL-6 [46]. Four hundred and twenty four sedentary, overweight/obese (BMI >28),

community-dwelling elderly (70-89 years) were randomized to treatment. The exercise intervention resulted in a significant 16% reduction in IL-6. CRP was 32% lower after exercise but was not statistically significantly different when compared to the health education group. There were no differences to exercise across sex. In subgroup analyses, they found that those with lower baseline functional status as determined by the Short Physical Performance Battery (SPPB) exhibited greater reductions in IL-6. Likewise, those with higher than median baseline IL-6 demonstrated larger reductions in IL-6. Interestingly, there was no change in body weight or percentage body fat (as measured by DXA) in either group over time. In contrast to their previous study on a different subject population, they concluded that regular aerobic exercise, even in the absence of weight loss, can be effective in reducing systemic IL-6; a factor associated with risk for disability and mortality. Aside from differences in subject populations (e.g. osteoarthritic patients vs. healthy older adult, the differences between this study and the one cited above are hard to reconcile and lend to the confusion as to whether weight loss is needed to reduce inflammatory biomarkers in response to exercise. In a follow up study using the same cohort but examining a wider array of inflammatory biomarkers, Beavers et al. (2010) found that IL-8 (a chemokine for neutrophils) was the only cytokine that was significantly reduced in the exercise group [43]. IL-6sR, IL-1sRII, sTNFr's I & II, IL-15, adiponectin, IL-1ra, IL-2sRα and TNF-α were all not affected.

In a study by Kohut et al (2006), sedentary, low fit older adults aged >64 years were randomized to moderate aerobic exercise training (65-80% heart rate reserve, 3x/wk, 30-45min/day) or flexibility control group for 10 months [47]. Exercisers had a significant reduction in serum CRP, IL-6 and IL-18 when compared to the flexibility group, whereas TNF-α declined in both groups. These anti-inflammatory effects of exercise were not related to various psychosocial factors (e.g. loneliness, perceived stress, depression, social support) or the use of β-adrenergic antagonists. These authors also included statin and aspirin use as covariates and found that these medications did not alter the exercise effect. Body weight and BMI did not change significantly in response to either intervention indicating an anti-inflammatory effect of exercise independent of weight loss. One limitation of all of the above studies was that none of them specifically examined changes in fat loss and its relation to changes in inflammation.

Our laboratory randomized 127 community-dwelling older adults (mean age 70 years) to 10 months of either cardiovascular exercise or flexibility/balance treatment and examined changes in CRP, body composition using dual X-ray absorptiometry, cardiovascular fitness and psychosocial variables [48]. We found that cardiovascular exercisers achieved a significant 13% reduction in CRP compared to no change in the flexibility/balance group. The reduction in CRP was significantly related to reductions in both percentage total body fat and trunk fat mass, but not with changes in cardiovascular fitness or changes in psychosocial variables. Linear regression revealed that only changes in trunk fat predicted changes in CRP. Thus, we concluded that ten months of cardiovascular exercise training in sedentary older adults reduced serum CRP and this effect was partially associated with reduced trunk fat. In support of the idea that changes in body fatness are necessary to reveal exercise-induced reductions in inflammation, using CRP as a primary inflammatory outcome in a randomized exercise trial in 61 healthy older adults (~66 years of age) Hammett et al (2004) found that 6 months of cardiovascular exercise did not result in changes in total body or trunk fat and had no effect on serum CRP, despite improving cardiovascular fitness[49]. It should be noted though that the baseline CRP in these subjects was quite low (~1.5mg/L).

Campbell et al (2009) examined the effects of 12 months of moderate (60-75% heart rate maximum) intensity exercise for 5 days/week vs. a stretching control group in 115 overweight or obese sedentary post-menopausal women aged ~60 years [50]. The intervention resulted in modest weight (e.g. -1.8Kg) and fat (e.g. -1.5%) loss and an improvement in aerobic fitness in the exercisers. There were no differences in caloric intake between groups. In an intent-to-treat analysis they found that exercisers realized a significant reduction in CRP at 12, but not 3 months, of intervention when compared to the control group that exhibited no change in CRP. Serum amyloid A (SAA; another hepatic acute phase inflammatory protein) was lower post-intervention in the exercisers; although this was not significant. IL-6 did not change in either group. Interestingly, the effect of exercise on CRP was restricted to women who were obese (BMI > 30kg/m^2) at baseline. Similar effects were seen when waist circumference was used as a measures of abdominal fat. Linear trends were observed between 12 month changes in aerobic fitness and intra-abdominal fat loss and CRP, but not SAA or IL-6. These data suggest that the exercise training that results in fat loss is effective at reducing CRP. What is encouraging is that only modest amounts of fat loss appear to be needed to reduce serum CRP. Kapasi et al (2003) found that 32 wks of functionally-oriented endurance and resistance exercise (2 hrs/day, 5 days/wk) which improved functional measures (e.g. walking distance and time etc.) had no effects on serum

neopterin or sTNFr-II in 190 frail elderly nursing home patients [51]. There was no mention of training-induced changes in body weight or fat mass in this and related published studies from this intervention.

Of all the randomized trials in older (>60yrs) subjects, it appears that training duration could be a factor for explaining whether exercise exerts or does not exert an anti-inflammatory effect. When the duration of the intervention was > 6 months, most [46-49], but not all[45] demonstrated reduced systemic inflammatory markers. When the training duration was 6 months or shorter exercise training had no influence on inflammatory markers [49, 52].

Longitudinal studies examining the influence of exercise on inflammation

In other non-randomized studies, In a large (n=277) study of Phase II cardiac rehabilitation exercise programs, Milani et al (2004) found 36% lower post-intervention CRP levels in exercisers versus sedentary controls [53]. The intervention improved cardiovascular fitness and modestly reduced BMI and body fat. It should be noted that cardiac patients typically have higher CRP levels than older adults not affected by heart disease and this may contribute to the large exercise-induced reductions. LeMaitre et al (2004) in a study of chronic stable heart failure patients (aged 62 yrs) comparing cycling exercise with electrical stimulation of the quadriceps and gastrocnemius muscles found that only cycling exercise resulted in reductions in sTNFr-II and a trend towards a reduction in sTNFr-I [54]. Serum CRP (3.67 vs. 3.27mg/L for pre- and post-training, respectively) and TNF-α (7.95 vs. 6.9 pg/mL for pre- and post-training, respectively) were lower in the cycling group, but not significantly so. Interestingly, both groups improved performance on walking and fatigue tests. No measures of changes in body weight or composition were noted in this study. Goldhammer et al (2005) found large (48%; 7.5 to 3.9 mg/L) reductions in serum CRP in 28 elderly coronary heart disease patients in response to 12 wks of aerobic exercise training as offered in typical Phase II cardiac rehabilitation programs [55]. Effects were also seen for IL-1, IL-6 and interferon-γ. The intervention resulted in small, non-significant changes in body weight and BMI. These results must be interpreted with caution as no control group was included in the study.

In addition to cardiovascular exercise, resistance training is another popular exercise intervention used to offset sarcopenia and loss of muscle function in the aged. The effects of strength training on inflammatory biomarkers have been examined in only a few studies. Bruunsgard et al (2004) examined the effects of 12 week of resistance training in a small group of frail nursing home residents on muscle strength and its relation to plasma TNF-α, IL-6 and sTNFR-I [56]. The training program improved muscle strength versus a control group but had no effect on any inflammatory marker. Body weight and composition were not reported. In another study in 21 elderly women, Ogawa et al (2010) found that 12 wk of strength training significantly reduced serum CRP and SAA despite having no effect on body weight or waist circumference [57]. IL-6 and TNF-α were unaffected. Interestingly, the change in muscle thickness was correlated to the change in CRP. This study suffered from lack of a comparison control group. In a direct comparison of the effects of aerobic versus resistance training, 45 sedentary elderly (~76 yrs) were randomized to either a cardiovascular exercise treatment (45 min, 3x/wk, 40-50% heart rate reserve), a resistance training treatment (elastic bands) or a sedentary control group for 16 wks with a 16wk follow up period [52]. Both aerobic and resistance training led to reductions in CRP when compared to the control group. Interestingly, the decrease did not occur immediately following the 16 wk of training but rather at the 32 wk follow-up period after 16 additional weeks of unregulated behavior. While there may have been some issue with increased physical activity during this period due to the time of year, the delayed effect of exercise needs to be further studied. There was only a modest correlation between waist circumference and CRP indicating that there may be other mechanisms accounting for the exercise-induced reduction in CRP.

Potential mechanisms of exercise training-induced reductions in inflammation in the aged

Given the evidence cited above, it can be concluded that exercise-induced loss of adipose tissue is related to exercise training-induced reductions in serum markers of inflammation. It is well-known that adipose tissue, especially visceral fat, of obese humans and animals produces pro-inflammatory cytokines that contribute in a large way to systemic inflammation [58, 59]. Adipose tissue from obese subjects contains higher levels of pro-inflammatory macrophages interspersed among adipocytes [60]. These cells can form multinucleate giant cells and can form 'crown-like' structures around dead or dying adipocytes [61]. Less is known about aged adipose, but there is evidence that visceral adipose tissue from old mice express higher mRNA levels of IL-1β, TNF-α and IL-6 when compared to the same fat depots in young mice [62]. In contrast to obesity where both adipocytes and stromovascular cells containing macrophages exhibit upregulated inflammation, aged adipocytes and not stromovascular cells appear to be the major pro-inflammatory cytokine producers in aged

adipose [62]. Our group has shown that, in high fat diet-fed obese mice, modest amounts of exercise training can reduce inflammatory gene expression in visceral adipose tissue [63, 64]. Therefore, it is logical to suspect that exercise training may have a similar effect on aged adipose tissue; although this has not yet been directly tested. It is noteworthy that caloric restriction also reduces markers of local and systemic inflammation in aging [65]and obesity [66] further lending evidence to the idea that fat loss contributes to reduced systemic inflammation.

There may also be other fat loss-independent mechanisms whereby exercise training might reduce systemic inflammation in the elderly. Acute exercise increases muscle production of IL-6 [67], and while IL-6 has been associated with inflammation, it also may have anti-inflammatory properties [68]. Starkie et al (2003) reported that exercise and IL-6 infusion could inhibit endotoxin-induced production of TNF-α in humans circumstantially suggesting that IL-6 can act in an anti-inflammatory fashion [69]. As exercise training is the accumulation of many individual acute exercise bouts, such acute increases in IL-6 may contribute to reduced chronic inflammation over the long-term. Another possibility is that regular exercise reduces oxidative stress by up-regulating endogenous anti-oxidant defense systems [2]. Overproduced oxidants like nitric oxide, peroxynitrite, and hydroxyl radical during aging are a major causative factor in activation of pro-inflammatory immune cells [70].

It is intriguing that some studies have shown that resistance training may reduce systemic inflammation. The mechanism responsible for this is unclear. However, Griewe et al (2001) found that TNF-α was elevated in muscles of frail elderly and 3 months of resistance exercise training reduced muscle TNF-α gene and protein expression [71]. Moreover, muscle protein synthesis rate was inversely related to TNF-α. It is unknown whether this exercise-induced reduction in skeletal muscle inflammation contributed to reduced systemic inflammation but this possibility exists and should be tested.

Work from Kevin Tracey's lab suggests that stimulation of the parasympathetic nervous system, via the efferent vagus nerve, inhibits pro-inflammatory cytokine production and protects against systemic inflammation [72]. They referred to this pathway as the "cholinergic anti-inflammatory pathway," and described it as a central homeostatic mechanism by which the sympathetic division of the autonomic nervous system stimulates the inflammatory response through the release of epinephrine and norepinephrine, while the parasympathetic nervous system works reciprocally to suppress this release of proinflammatory cytokine [72]. A primary function of the vagus nerve is to control heart rate, which is typically measured by heart rate recovery (HRR) following exercise and heart rate variability (HRV). A major adaptation to long-term cardiovascular exercise training is a decrease in HRR and HRV. Thus, aerobic exercise training may increase efferent vagus nerve activity, and this increased activity may contribute to the anti-inflammatory effect of exercise. This hypothesis is supported by our cross sectional study which demonstrated HRR was the best predictor of CRP in aged adults[73], however, it has not been definitely tested.

In summary, regular exercise reduces fat mass and adipose tissue inflammation which is known to contribute to systemic inflammation [58, 59]. Independent of losses of fat mass, exercise also increases muscle production of IL-6 which is known to reduce TNF-α production and increase anti-inflammatory cytokines [69]. Exercise training also increases vagal tone [74], which according to the cholinergic anti-inflammatory reflex espoused by Tracy [72], could lead to reductions in systemic inflammation. Acute exercise activates the hypothalamic-pituitary-adrenal axis and sympathetic nervous systems. Cortisol is known to have potent anti-inflammatory effects [75], and catecholamines can inhibit pro-inflammatory cytokine production [76]. Several studies [77] have demonstrated that exercise training can down regulate toll-like receptor 4, ligation of which activates pro-inflammatory cascades [78] . In summary, exercise training is known to have beneficial effects across a broad spectrum of organ systems and its anti-inflammatory actions are complicated by the intricate interplay among organs and cytokines. Although not all of the mechanisms mentioned above have been demonstrated to operate in the aged, it is very likely that several of the aforementioned mechanisms, and others not discovered, are at play.

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